REMARKS

Applicants submit this response to the Office Action dated September 6, 2006. Claims 1-30, 43, and 44 have been cancelled. The amendment to claim 31 is discussed below, and no new matter is added.

Claims 31-42 were rejected under 35 U.S.C. § 102(b) as being anticipated by Danilenko et al., SU 539878, 1976. The reference allegedly discloses a compound having antiphlogistic activity. As applicants argued in the response filed on June 19, 2006, the Examiner provided no evidence that Danilenko et al. describe a "method of antagonizing chemokine receptors." The reference is in Russian and only the translated title and one-sentence abstract were provided. The Examiner states that the compound disclosed in the reference reads on compounds in which n is 0, R_5 is H, R_2 is H, and R_3 is aryl.

Without acquiescing to the ground of rejection, applicants submit that claim 31 as amended, and claims 32-42, which depend upon claim 31, are not subject to this ground of rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 31-42 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for some inhibiting data as given in Table 6, allegedly does not reasonably provide enablement for 1) antagonizing chemokine receptors, 2) inhibiting a chemokine mediated cellular "event," 3) inhibiting IL8, GRO-alpha driven neutrophil chemotaxis, 4) treating a disorder selected from IBD, psoriasis, ARDS, cancer, atherosclerosis, reperfusion injury, 5) inhibiting a G-protein-coupled, 7TM receptor, 6) modulating binding of peptide YY to a NPY receptor, 7) modulating the binding of a somatostatin to a somatostatin cell receptor, or 8) treating, through a therapeutically or prophylactically acceptable manner, an inflammatory "event."

Applicants previously argued that the specification does provide enablement for antagonizing chemokine receptors. Examples 21 and 22 provide for a number of compounds that antagonize chemokine receptors by decreasing binding of [^{125}I]Interleukin-8. Example 21 discloses a large number of compounds that have been tested with the CXCR2 receptor, and Example 22 discloses nine compounds that have been tested with five different chemokine receptors, including the CXCR2 receptor.

Applicants further argued that the specification provides enablement for inhibiting a chemokine mediated cellular "event." GRO-alpha driven neutrophil chemotaxis is an example of a chemokine-mediated cellular event. Example 21 discloses a large number of compounds that have been tested in an assay designed to measure neutrophil chemotaxis, and the data show a significant number of these that affect this process.

Applicants argued that the specification does provide enablement for treating a disorder such as IBD, psoriasis, ARDS, cancer, atherosclerosis, or reperfusion injury. A number of inflammation-related disorders have been shown to be associated with elevated levels of IL-8 and concomitant activation of CXCR1 and CXCR2 receptors. As outlined on page 3, lines 22-26, psoriasis is associated with high levels of IL-8. Similar associations are described for ARDS (page 2, lines 18-28), cancer (page 2, lines 26-27), and atherosclerosis (page 3, lines 11-16). IBD and reperfusion injury are disorders that are generally related to inflammation and likely involve similar receptor pathways. The assays described in Examples 21 and 22 demonstrate that a number of compounds have biological activity directly related to these disorders.

Applicants further argued that the specification provides enablement for inhibiting a G-protein-coupled, 7TM receptor. GRO-alpha driven chemotaxis is an example of a process that is mediated by a G-protein-coupled 7TM receptor. Example 21 provides data showing compounds that inhibit this process. Further, the chemotaxis data was obtained using cells obtained from human blood, not an *in vitro* cell culture system.

Applicants also argued that the specification is enabling for modulating the binding of Peptide YY to an NPY receptor. Example 21 discloses three such compounds that inhibit binding of Peptide YY to an NPY receptor. Similarly, Example 21 discloses a compound that inhibits binding of somatostatin to a somatostatin cell receptor.

Additionally, applicants argued that the specification provides enablement for the treatment, through a therapeutically or prophalactically acceptable manner, of an inflammatory "event." The disorders described in the application may be described as inflammatory "events." The biological activities demonstrated in Examples 21 and 22 have been shown to correlate with inflammatory disorders as described on pages 2 and 3 in the specification.

The eight Wands factors are discussed below, with reference to the present Office Action.

1. *The breadth of the claims.* The Examiner states at page 3, paragraph 1, that the compounds cover a wide range of compounds. This is the case with pharmaceutical claims, and the presence of potentially non-operative embodiments does not defeat enablement.

The Examiner cited Genentech Inc. v. Novo Nordisk and quotes the "hunting license" analogy from Brenner v. Hanson, 148 U.S.P.Q. 689, 696 (1966). As applicants previously argued, this language related to a utility requirement, and so its application to an enablement issue is inappropriate. Furthermore, citing a utility-related quote from Brenner ignores the fact that the underlying situation in Genentech fails to support lack of enablement of the present claims. As the Genentech Court stated,

> Novo further argues that neither the specification nor the references cited by Genentech suggest a single amino acid sequence, out of the virtually infinite range of possibilities. 42 U.S.P.Q. at 1004.
>
> [W]hen there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required. 42 U.S.P.Q. 2d at 1005. (Emphasis added.)

The present specification and claims do not fall into this category, and Genentech Inc. v. Novo Nordisk fails to support the alleged lack of enablement. The Examiner cited Genentech again in the present Office Action without addressing applicants' arguments as to the inapplicability of the case to the present factual situation.

2. *Nature of the invention.* The nature of the invention involves assays and assay interpretation that are well-known to those of ordinary skill in the art. The Court in Wands stated that the nature of monoclonal antibody technology is that it involves screening, including screening of negative samples (in that case, hybridomas). The number of potentially negative samples was not viewed as a determining factor in reaching a finding of undue experimentation. (8 U.S.P.Q. 2d at 1406-1407)

By analogy, the assays described in the specification refer to methods published in well-known journals, such as those cited on pages 64-66. Because the invention is in

the pharmaceutical arts, one of skill would expect to perform further work to adapt the disclosed methods and compounds to *in vivo* use. The Examiner stated (page 3, paragraph 2) that the nature of the invention is "a (highly) substituted compound that is useful to treat and inhibiting various receptors." Applicants disagree with characterizing the invention as inhibiting "various receptors" when the disclosure teaches chemokine receptors.

3. *The state of the prior art*. The Wands Court found that "all the methods needed to practice the invention were well known." (8 U.S.P.Q. 2d at 1406.) Similarly, the methods of assaying the activity of compounds and interpreting the assay results are well known. These well-known assays are applied to the novel compounds for the methods claimed in claims 31 and 32. The Examiner states that "there is no absolute predictability and no established correlation between *in vitro* activity and the treatment of various diseases and also the IC50 values, as in the *in vitro* data is not a reliable predictor of success even in view of the seemingly high level of skill in the art."

The Examiner also states that inhibiting cellular events or treating disease related to chemokine receptors and G protein–coupled receptors is "not an absolute predictability." (Page 4, lines 18-19.) Absolute predictability is not the standard under Wands. The Examiner again cited Cummings, C.J., J. Immunol. 162:2341-2346 (1999) to support the alleged complication of selecting therapeutic targets to reduce inflammation. However, as applicants argued previously, the article actually helps to simplify the process. At page 2345, the last paragraph states,

> These data simplify an otherwise complex and redundant system of CXC chemokines and receptors and focus attention on the importance of CXCR1 in sepsis. These studies suggest that a CXCR1 receptor-targeted strategy to limit inflammation in patients with sepsis will reduce PMN migration to CXC chemokines, yet preserve PMN responsiveness to bacterial products.

Furthermore, the teachings of Cummings, which was published several years before the filing date of this application, form part of the background knowledge of those of skill practicing the invention. The paper also states that the observations extend previous findings and "demonstrate their relevance to human disease." (Page 2345, lines 35-37.)

In the present Office Action, the Examiner simply cited the article again without addressing applicants' comments on the article. Applicants therefore reiterate the arguments above.

4. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (3) and (4) above. The Wands Court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the Court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the Court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations, 8 U.S.P.Q. 2d at 1406. By analogy, it would not defeat enablement for one of skill in the present art to test the compounds disclosed for use in the disease states and conditions as claimed. As the Examiner again notes, "the ordinary artisan is highly skilled." (Page 4, paragraph 4.)

5. *The predictability or unpredictability of the art.* Regarding the level of predictability in the art, the Examiner states that the pharmaceutical art is unpredictable, and again cites In re Fisher, 427 F. 2d 833, 166 U.S.P.Q. 18 (CCPA 1970).

First, the Examiner states "that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity," at page 4 of the Office Action, paragraph 5. Applicants previously respectfully requested that the Examiner provide statutory or case law support for that statement, and none has been provided.

Second, as applicants previously argued, In re Fisher is not on point for the present issue. Fisher does state that the scope of enablement varies inversely with the degree of unpredictability of the factors involved. However, this was in reference to claim limitations on potency of the materials, in that case a biological preparation of ACTH (adrenocorticotrophic hormone).

The claims recited a potency of "at least 1" International unit per milligram. The Court questioned whether an inventor should dominate "future compositions having potencies far in excess of those obtainable from his teachings plus ordinary skill." (427

F.2d at 839.) The Court also noted that the recitation was "open ended" with no upper limit. This fact pattern is distinct from the present situation in which a finite, closed set of compounds is recited in claim 31 and the claims depending thereon.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. The Examiner has provided no evidence that the testing of additional compounds of the invention would be "more difficult or unreliable" (8 U.S.P.Q. 2d at 1406) than for those tested according to the Examples. One of skill in this art expects to conduct extensive experimentation for the very reasons mentioned by the Examiner, such as the effect of the R groups.

6. *Amount of direction or guidance provided.* Regarding the amount of direction provided by the inventors, the Examiner again stated that "there are no examples with the R being heterocyclic groups and also there is no data provided to show that these compounds do indeed treat various diseases." (Page 4, paragraph 6.) However, the sixth and ninth compounds on page 51 as well as the last compound on page 58 are heterocyclic compounds that were tested in the IL-8 binding assay and the GRO-α ChTx assay.

The specification provides clear directions for performing the experimentation, and cites to published scientific articles for details not mentioned in the specification. Similarly, the Wands Court found that the starting material was available to the public (as is the material used in the present application) and the patent at issue in Wands provided a detailed description of the methods. (8 U.S.P.Q. 2d at 1404, 1405.) Paragraph 6 of the present Office Action is a repeat of the previous Office Action, with no reply to applicants' arguments.

7. *Presence of absence of working examples.* Regarding the "existence of working examples," the Examiner states that the specification only discloses nine examples "with a few assays." Applicants previously noted that Tables 3-6 show that 95 compounds were tested. In any event, Wands permits experimentation as long as it is not undue. One of skill can routinely test other compounds as described in the

Examples. In the present Office Action, the Examiner simply reiterated the previous comments, with no reply to applicants' arguments.

8. Quality of experimentation necessary. The Examiner states that it is not clear "who the patient in need there of" is (page 5, line 4). On the contrary, applicants pointed out in the previous response that several well-known disease states are associated with activation of CXCR1 and CXCR2 receptors, particularly in association with elevated levels of IL-8. The method of the claims relies on this underlying disease mechanism. As in all pharmaceutical research, some members of the claimed class of molecules may not be effective. However, encountering negative results would not mean that undue experimentation is involved, according to Wands.

In view of the foregoing remarks, applicants submit that the Examiner has not met her burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Commissioner is hereby authorized to charge the required fees to Deposit Account No. 04-0258. If additional fees are believed necessary, the Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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